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FILING DATE: *February 11, 2004*
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Certified by

Jon W. Dudas

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PTO/SB/16 (10-01)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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☒ *Additional inventors are being named on the 1 separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

COMPOUNDS AND COMPOSITIONS AS LXR MODULATORS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 53 ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☒ Other (specify) RETURN POSTCARD AND FEE TRANSMITTAL

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

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☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 50-1885 — 160

☐ Payment by credit card. Form PTO-2038 is attached.

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____.

Respectfully submitted,

SIGNATURE Scott W. Reid.

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TELEPHONE 858-812-1796

Date 2/11/04

REGISTRATION NO. *(if appropriate)* 48,097

Docket Number: P1140US00

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

PROVISIONAL APPLICATION COVER SHEET

Additional Page

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Docket Number	P1140US00

INVENTOR(S)/APPLICANT(S)

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Number 1 of 1

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TOTAL AMOUNT OF PAYMENT ($) 160

Complete if Known	
Application Number	
Filing Date	11 February 2004
First Named Inventor	Valentina MOLTENI
Examiner Name	
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METHOD OF PAYMENT (check all that apply)

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☒ Deposit Account:

Deposit Account Number: 50-1885

Deposit Account Name: The Genomics Institute of the Novartis Research Foundation

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	160
1002	330	2002	165	Design filing fee	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
1005	160	2005	80	Provisional filling fee	

SUBTOTAL (1) ($) 160

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20 **	= 0	X		=	0
Independent Claims		-3 **	= 0	X		=	0
Multiple Dependent				X		=	0

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

**or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

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Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,300	2453	650	Petition to revive – unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17 (q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 0

SUBMITTED BY				Complete *(if applicable)*	
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Signature	Scott W. Reid			*Date*	11 February 2004

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By: _____
Scott W. Reid

Docket No: P1140US00

United States Provisional Patent Application

COMPOUNDS AND COMPOSITIONS AS LXR MODULATORS

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COMPOUNDS AND COMPOSITIONS AS LXR MODULATORS

BACKGROUND OF THE INVENTION

Field of the Invention

The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of liver X receptors (LXRs).

Background

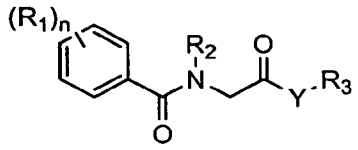
Liver X receptors (LXRs), LXRα and LXRβ, are nuclear receptors that regulate the metabolism of several important lipids, including cholesterol and bile acids. While LXRβ is expressed ubiquitously in the body, LXRα is expressed in the liver and to a smaller degree in the kidneys, small intestine, adipose tissue, spleen and adrenal glands.

LXRs bind to the ATP binding cassette transporter-1 (ABCA1) promoter and increase expression of the gene to produce ABCA1 protein. ABCA1 is a membrane bound transport protein that is involved in the regulation of cholesterol efflux from extra-hepatic cells onto nascent high-density lipoprotein (HDL) particles. Mutations in the ABCA1 gene result in low levels of HDL and an accompanying increased risk of cardiovascular diseases such as atherosclerosis, myocardial infarction and ischemic stroke. LXRα and β agonists have been shown to increase ABCA1 gene expression thereby increasing HDL cholesterol and, as a consequence, decreasing both the net absorption of cholesterol and the risk of cardiovascular disease. LXR agonists also upregulate macrophage expression of apolipoprotein E (apoE) and ABCG1, both of which contribute to the efflux of cellular cholesterol. By stimulating macrophage cholesterol efflux through upregulation of ABCA1, ABCG1 and/or apoE expression, as well as increasing the expression of other target genes including cholesterol ester transfer protein and lipoprotein lipase, LXR agonists influence plasma lipoproteins.

The novel compounds of this invention modulate the activity of LXRs and are, therefore, expected to be useful in the treatment of LXR-associated diseases such as cardiovascular diseases, inflammation and disorders of glucose metabolism such as insulin resistance and obesity.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds of Formula I:



in which:

Y is chosen from –O–, –NR_4– and –S–; wherein R_4 is chosen from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl-C_{0-4}alkyl, C_{3-8}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl;

n is chosen from 0, 1, 2, 3 and 4;

R_1 is chosen from halo, hydroxy, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy, -$XC(O)R_4$, -$XOC(O)R_4$, -$XC(O)OR_4$, -XOR_4, -$XS(O)_2R_4$, -$XS(O)R_4$, -XSR_4, -XNR_4R_8, -$XC(O)NR_4R_8$, -$XNR_4C(O)R_4$, -$XNR_4C(O)OR_4$, -$XNR_4C(O)NR_4R_8$, -$XNR_4C(NR_4R_4)NR_4R_8$, -$XP(O)(OR_4)OR_4$, -$XOP(O)(OR_4)OR_4$, -$XS(O)_2NR_4R_8$, -$XS(O)NR_4R_8$, -$XSNR_4R_8$, -$XNR_4S(O)_2R_4$, -$XNR_4S(O)R_4$, -XNR_4SR_4, -$XNR_4C(O)NR_4R_8$, - and -$XC(O)SR_4$; wherein X is a bond or C_{1-6}alkylene; and R_4 and R_8 are independently chosen from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl-C_{0-4}alkyl, C_{3-8}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; or R_4 and R_8 together with the nitrogen atom to which R_4 and R_8 are attached form C_{5-10}heteroaryl or C_{3-8}heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_4 or the combination of R_4 and R_8 is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{3-8}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any aryl-alkyl, heteroaryl-alkyl, cycloalkyl-

alkyl or heterocycloalkyl-alkyl of R_2 is optionally substituted by 1 to 4 radicals chosen from halo, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{3-8}heteroaryl, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, $-XC(O)R_5$, $-XOC(O)R_5$, $-XC(O)OR_5$, $-XOR_5$, $-XS(O)_2R_5$, $-XS(O)R_5$, $-XSR_5$, $-XNR_5R_8$, $-XC(O)NR_5R_8$, $-XNR_5C(O)R_5$, $-XNR_5C(O)OR_5$, $-XNR_5C(O)NR_5R_8$, $-XNR_5C(NR_5R_8)NR_5R_8$, $-XP(O)(OR_5)OR_5$, $-XOP(O)(OR_5)OR_5$, $-XS(O)_2NR_5R_8$, $-XS(O)NR_5R_8$, $-XSNR_5R_8$, $-XNR_5S(O)_2R_5$, $-XNR_5S(O)R_5$, $-XNR_5SR_5$, $-XNR_5C(O)NR_5R_8$, $-XR_6$ and $-XOR_7$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent of R_2 is optionally substituted by 1 to 3 radicals chosen from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-XC(O)R_5$, $-XOC(O)R_5$, $-XC(O)OR_5$, $-XOR_5$, $-XS(O)_2R_5$, $-XS(O)R_5$, $-XSR_5$, $-XNR_5R_8$, $-XC(O)NR_5R_8$, $-XNR_5C(O)R_5$, $-XNR_5C(O)OR_5$, $-XNR_5C(O)NR_5R_8$, $-XNR_5C(NR_5R_8)NR_5R_8$, $-XP(O)(OR_5)OR_5$, $-XOP(O)(OR_5)OR_5$, $-XS(O)_2NR_5R_8$, $-XS(O)NR_5R_8$, $-XSNR_5R_8$, $-XNR_5S(O)_2R_5$, $-XNR_5S(O)R_5$, $-XNR_5SR_5$, $-XNR_5C(O)NR_5R_8$, $-XR_6$ and $-XOR_7$; wherein X is a bond or C_{1-6}alkylene; R_5 and R_8 are independently chosen from hydrogen and C_{1-6}alkyl; or R_5 and R_8 together with the nitrogen to which R_5 and R_8 are attached form C_{3-8}heteroaryl or C_{3-8}heterocycloalkyl; wherein any heteroaryl or heterocycloalkyl of the combination of R_5 and R_8 is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; R_6 is chosen from cyano and C_{1-6}alkyl; and R_7 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{3-8}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_7 is optionally further substituted by $-XC(O)OR_5$; wherein R_5 is chosen from hydrogen and C_{1-6}alkyl;

R_3 is chosen from C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

In a second aspect, the present invention provides a pharmaceutical composition which contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of LXR activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which LXR activity contributes to the pathology and/or symptomology of the disease.

In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be either straight-chained or branched. C_{1-6}alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

"Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl can be phenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group. "Heteroaryl" is as defined for aryl where one or more of the ring members are a heteroatom. For example heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc. "C_{6-10}arylC_{0-4}alkyl" means an aryl as described above connected via a alkylene grouping. For example, C_{6-10}arylC_{0-4}alkyl includes phenethyl, benzyl, etc.

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C_{3-10}cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

"Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O) -, -S-, -S(O) - or -$S(O)_2$-, wherein R is hydrogen, C_{1-4}alkyl or a nitrogen protecting group. For example, C_{3-8}heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, etc.

"Halogen" (or halo) preferably represents chloro or fluoro, but can also be bromo or iodo.

The term "modulate" with respect to an LXR receptor refers to activation of the LXR receptor and its biological activities associated with the LXR pathway (e.g., transcription regulation of a target gene). Modulation of LXR receptor can be up-regulation (i.e., agonizing, activation or stimulation) or down-regulation (i.e. antagonizing, inhibition or suppression). The mode of action of an LXR modulator can be direct, e.g., through binding to the LXR receptor as a ligand. The modulation can also be indirect, e.g., through binding to and/or modifying another molecule which otherwise binds to and activates the LXR receptor. Thus, modulation of LXR includes a change in the bioactivities of an LXR agonist ligand (i.e., its activity in binding to and/or activating an LXR receptor) or a change in the cellular level of the ligand.

"Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

The present invention provides compounds, compositions and methods for the treatment of diseases in which modulation of LXR activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I.

In one embodiment, with reference to compounds of Formula I, n is chosen from 0, 1, 2 and 3.

In another embodiment, R_1 is chosen from halo, C_{1-6}alkyl and halo-substituted-C_{1-6}alkyl.

In another embodiment, R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{3-8}heteroaryl-C_{0-4}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; wherein any aryl-alkyl, heteroaryl-alkyl or cycloalkyl-alkyl of R_2

is optionally substituted by 1 to 3 radicals chosen from halo, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{3-8}heteroaryl, C_{3-8}heterocycloalkyl, $-XC(O)R_5$, $-XC(O)OR_5$, $-XOR_5$, $-XSR_5$, $-XNR_5R_8$, $-XC(O)NR_5R_8$, $-XNR_5C(O)R_5$, $-XR_6$ and $-XOR_7$; wherein any aryl, heteroaryl or heterocycloalkyl substituent of R_2 is optionally substituted by 1 to 3 radicals chosen from halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-XC(O)OR_5$, $-XOR_5$, $-XS(O)_2R_5$, $-XNR_5C(O)R_5$, $-XNR_5C(O)OR_5$, $-XR_6$ and $-XC(O)R_7$; wherein X is a bond or C_{1-6}alkylene; R_5 and R_8 are independently chosen from hydrogen and C_{1-6}alkyl; R_6 is cyano; and R_7 is C_{6-10}aryl-C_{0-4}alkyl optionally further substituted by $-XC(O)OR_5$; wherein R_5 is chosen from hydrogen and C_{1-6}alkyl; and R_3 is C_{1-6}alkyl.

In another embodiment, R_1 is chosen from halo, methyl, ethyl and trifluoromethyl; and R_3 is *t*-butyl.

In a further embodiment, R_2 is chosen from phenyl, benzo[1,3]dioxolyl, cyclopentyl, 1H-indolyl, naphthyl and 2-oxo-2,3-dihydro-1H-indol-5-yl; wherein any aryl-alkyl, heteroaryl-alkyl or cycloalkyl-alkyl of R_2 is optionally substituted by 1 to 3 radicals chosen from halo, hydroxy, methoxy, trifluoro-methoxy, trifluoro-methyl, methyl, phenyl, oxazolyl, pyrazolyl, pyrimidinyl, amino-carbonyl, dimethyl-amino, thiophenyl, methyl-sulphanyl, methyl-formamidyl, methyl-carbonyl, ethenyl, phenoxy, methoxy-carbonyl, benzoxy, isopropyl, furanyl, isopropyloxy, [1,3]dioxolanyl and cyano-methyl; wherein any aryl, heteroaryl or heterocycloalkyl substituent of R_2 is optionally substituted by 1 to 3 radicals chosen from halo, methyl, cyano, carboxy, carboxy-methyl, cyano-methyl, methoxy, phenyl, acetyl-amino, methyl-sulphonyl, methoxy-carbonyl-amino, 1-carboxy-ethyl and trifluoro-methoxy.

Preferred compounds of Formula I are detailed in the Examples and Table I, *infra*.

Pharmacology and Utility

Compounds of the invention modulate the activity of LXRs and, as such, are useful for treating diseases or disorders in which LXRs contribute to the pathology and/or symptomology of the disease. This invention further provides compounds of this invention for use in the preparation of medicaments for the treatment of diseases or disorders in which LXRs contribute to the pathology and/or symptomology of the disease. LXR mediated diseases or conditions include inflammation, cardiovascular disease including atherosclerosis, arteriosclerosis,

hypercholesteremia, hyperlipidemia and disorders of glucose homeostasis, including insulin resistance, type II diabetes, and obesity.

Lipoprotein metabolism is a dynamic process comprised of the production of triglyceride and cholesterol rich particles from the liver as very low-density lipoprotein (VLDL), modification of these lipoprotein particles within the plasma (VLDL to intermediate density (IDL) to low-density lipoprotein (LDL)) and clearance of the particles from the plasma, again by the liver. This process provides the transport of triglycerides and free cholesterol to cells of the body. Reverse cholesterol transport is the proposed mechanism by which excess cholesterol is returned to the liver from extra-hepatic tissue.

The process is carried out by high-density lipoprotein (HDL) cholesterol. The combination of lipoprotein production (VLDL, HDL) from the liver, modification of particles (all) within the plasma and subsequent clearance back to the liver, accounts for the steady state cholesterol concentration in plasma. Compounds of this invention increase reverse cholesterol transport by increasing cholesterol efflux from the arteries. This invention includes the use of compounds of this invention for the preparation of a medicament for increasing reverse cholesterol transport. Additionally, this invention provides compounds for inhibiting cholesterol absorption and the use of compounds of this invention for the preparation of a medicament for inhibiting net cholesterol absorption.

The compounds of this invention can also be useful for the prevention or treatment of inflammation and neurodegenerative diseases or neurological disorders. Accordingly, this invention also provides a method for preventing or treating inflammation and a method for preventing or treating neurodegenerative diseases or neurological disorders, particularly neurodegenerative diseases or disorders characterized by neuron degeneration, neuron injury or impaired plasticity or inflammation in the CNS. Particular diseases or conditions that are characterized by neuron degeneration and inflammation, and thus benefiting from the growth and/or repair of neurons include stroke, Alzheimer's disease, fronto-temporal dementias (tauopathies), peripheral neuropathy, Parkinson's disease, dementia with Lewy bodies, Huntington's disease, amyotrophic lateral sclerosis and multiple sclerosis. Diseases or conditions that are characterized by neuron degeneration and/or impaired plasticity include psychiatric disorders such as schizophrenia and depression. Particular diseases or conditions that are characterized by neuronal injury include those conditions associated with brain and/or spinal

cord injury, including trauma. In addition, the compounds of this invention can be used to treat or prevent various diseases with an inflammatory component, such as rheumatoid arthritis, osteoarthritis, psoriasis, asthma, etc.

LXR agonists improve glucose tolerance and enhance glut4 expression (U.S. Provisional Patent Application 60/436,112, filed 12/23/2002; U. S. Patent Application 10/745,334, filed 12/22/2003). There is a coordinated regulation of genes involved in glucose metabolism in liver and adipose tissue. In the liver, LXR agonists inhibit expression of several genes that are important for hepatic gluconeogenesis, e.g., PGC-1, phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase expression. Inhibition of these gluconeogenic genes is accompanied by an induction in expression of glucokinase, which promotes hepatic glucose utilization. It was also found that glut4 mRNA levels were upregulated by LXR agonists in adipose tissue, and that glucose uptake in 3T3-L1 adipocytes was enhanced in vitro.

In accordance with these discoveries, the present invention provides methods for enhancing glut4 expression in cells in a subject by administering a compound of the invention to the subject. The present invention also provides methods for treating diabetes mellitus and related disorders, such as obesity or hyperglycemia, by administering to a subject an effective amount of a compound of the invention to ameliorate the symptoms of the disease. For example, type II diabetes is amenable to treatment with methods of the present invention. By enhancing sensitivity to insulin and glucose uptake by cells, administration with a compound of the invention can also treat other diseases characterized by insulin dysfunction (e.g., resistance, inactivity or deficiency) and/or insufficient glucose transport into cells.

Compounds of the present invention also regulate expression levels of a number of genes that play important roles in liver gluconeogenesis. Accordingly, the present invention further provides methods for reducing gluconeogenesis in a subject by modulating expression of such genes (e.g., PGC-1 and PEPCK).

In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount (*See, "Administration and Pharmaceutical Compositions", infra*) of a compound of Formula I or a pharmaceutically acceptable salt thereof. For any of the above uses, the required

dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Administration and Pharmaceutical Compositions

In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, conveniently administered, e.g. in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50mg active ingredient.

Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrollidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions can be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting

or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they can also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present invention with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations can also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations). For example, synergistic effects can occur with other substances used in the treatment of cardiovascular, inflammatory and/or neurodegenerative diseases. Examples of such compounds include fibrates, TZDs, metformin, etc. Where the compounds of the invention are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

The invention also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the

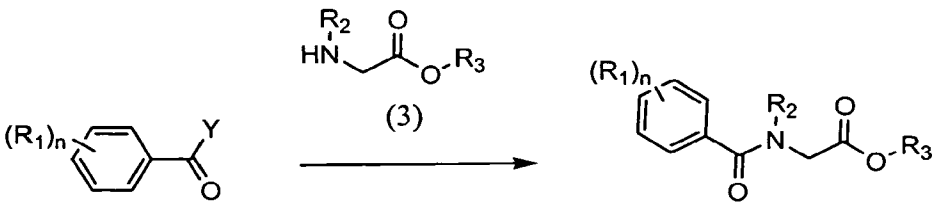
active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Processes for Making Compounds of the Invention

The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

Compounds of Formula I can be prepared by proceeding as in the following Reaction Scheme I:

Reactions Scheme I



(2) (I)

in which N, R_1, R_2 and R_3 are as defined for Formula I in the Summary of the Invention. Compounds of Formula I are prepared by reacting a compound of formula 2 with a compound of formula 3 in the presence of a suitable solvent (e.g., dichloromethane, or the like) and a suitable base (e.g., diisopropylethylamine, or the like). The reaction is carried out in the temperature range of 10 to 40°C and takes up to 20 hours to complete.

Additional Processes for Making Compounds of the Invention

A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.)

Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present

invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

In summary, the compounds of Formula I can be made by a process, which involves:

(a) that of reaction scheme I; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

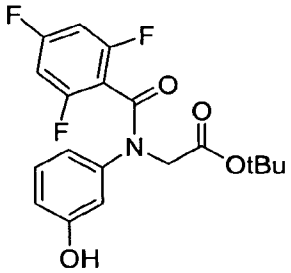
One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

The present invention is further exemplified, but not limited, by the following examples that illustrate the preparation of compounds of Formula I according to the invention.

Example 1

Tert-butyl 2-(2,4,6-trifluoro-N-(3-hydroxyphenyl)benzamido)acetate



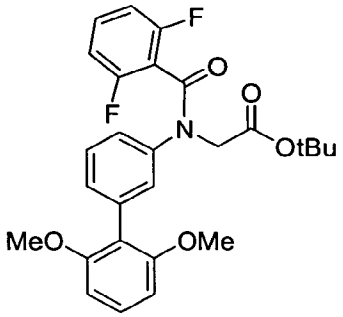
To a solution of 3-aminophenol (4.58 mmol) in DMF (15 mL) is added N,N-diisopropylethyl amine (4.58 mmol) and *tert*-butylbromoacetate (4.58 mmol) and the reaction mixture is stirred at 50 °C for 2 hours. Ethyl acetate and water are added to the reaction mixture and the phases are separated. The organic phase is dried on sodium sulfate, filtered and the solvent evaporated. The *tert*-butyl 2-(3-hydroxyphenylamino) acetate obtained is used as such in the next step without further purification.

To a solution in CH_2Cl_2 (15 mL) of *tert*-butyl 2-(3-hydroxyphenylamino)acetate obtained in the previous step, is added N,N-diisopropylethyl amine (9.16 mmol) followed by dropwise addition of 2,4,6-trifluorobenzoyl chloride (9.16 mmol). The reaction mixture is stirred for 12 hours at room temperature. After concentration and redissolution in DMSO, the residue is

purified by preparative LCMS (10 to 90% CH_3CN) to give *tert*-butyl 2-(2,4,6-trifluoro-N-(3-hydroxyphenyl)benzamido)acetate in 25% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (t, J = 8.4 Hz, 1H), 6.78 (s, 2H), 6.69 (d, J = 8 Hz, 1H), 6.48 (t, J = 8 Hz, 2H), 5.85 (bs, 1H), 4.42 (s, 2H), 1.49 (s, 9H); MS: (ES^+) 382.1 $(M+1)^+$.

Example 2

Tert-butyl 2-(N-(3-(2,6-dimethoxyphenyl)phenyl)-2,6-difluorobenzamido)acetate



To a solution of 3-bromoaniline (69.8 mmol) in 200 mL of CH_2Cl_2 under nitrogen atmosphere, is added N,N-diisopropylethyl amine (69.8 mmol) followed by dropwise addition of 2,6-difluorobenzoylchloride (69.8 mmol). The reaction mixture is stirred at room temperature for 5 hours. TLC (hexanes: ethyl acetate = 8:2) and analytical LCMS (20 to 100% CH_3CN) reveal the complete conversion of the starting material to the product. Water is added to the reaction mixture and the phases are separated. The organic layer is dried on sodium sulfate, filtered and the solvent is evaporated. The product, N-(3-bromophenyl)-2,6-difluorobenzamide, is used without further purification in the next step.

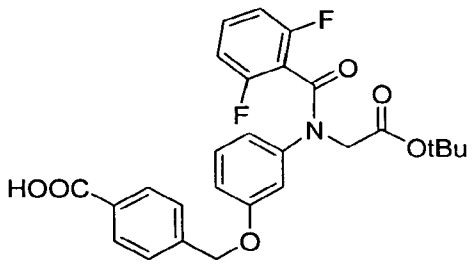
To a solution of N-(3-bromophenyl)-2,6-difluorobenzamide in 200 mL of DMF at room temperature and under nitrogen atmosphere, NaH 60% in oil dispersion (104.7 mmol) is slowly added and the reaction mixture is stirred for 30 minutes. *Tert*-butylbromoacetate (104.7 mmol) is added and the reaction stirred at room temperature. After 12 hours the reaction is complete by TLC (hexanes: ethyl acetate = 8: 2) and analytical LCMS (20 to 100% CH_3CN). Ethyl acetate and water are added to the reaction mixture and the phases are separated. The organic phase is dried on sodium sulfate, filtered and the solvent is evaporated. The crude is purified by automated column chromatography (gradient of hexanes and ethyl acetate) to give *tert*-butyl 2-(N-(3-bromophenyl)-2,6-difluorobenzamido)acetate in 75% yield: ^1H NMR (400

MHz, $CDCl_3$) δ 7.36 (bs, 1H), 7.20 (m, 1H), 7.07(m, 2H), 6.96 (t, J = 8 Hz, 1H), 6.62 (td, J_1 = 8 Hz, J_2 = 1.2 Hz), 4.32 (s, 2H), 1,39 (s, 9H); MS: (ES^+) 448.0 $(M+23)^+$.

Tert-butyl 2-(N-(3-bromophenyl)-2,6-difluorobenzamido)acetate (0.55 mmol) is mixed with 2,6-dimethoxyphenyl boronic acid (6.13 mmol) and $Pd(Ph_3P)_4$ (0.024 mmol). To the solid mixture under nitrogen, Na_2CO_3 2M (0.83 mL) is added followed by DMF (5.6 mL). The reaction mixture is stirred at room temperature for 1 hour and then heated at 85°C for 12 hours. The reaction mixture is purified by automated column chromatography (gradient of hexanes and ethyl acetate) to give *tert*-butyl 2-(N-(3-(2,6-dimethoxyphenyl)phenyl)-2,6-difluorobenzamido)acetate (Yield: 55%): ^1H NMR (400 MHz, $CDCl_3$) δ7.19 (m, 6H), 6.69 (t, J = 7.2 Hz, 2H), 6.58 (d. J = 8.4 Hz, 2H), 4.46 (s, 2H), 3.64 (s, 6H), 1,48 (s, 9H); MS: (ES^+) 484.1 $(M+23)^+$.

Example 3

Tert-butyl 2-(2,6-difluoro-N-(3-(4-carboxybenzyloxy)phenyl)benzamido)acetate



To a solution of 3-aminophenol (6.98 mmol) in 20 mL of CH_2Cl_2 under nitrogen atmosphere, is added N,N-diisopropylethyl amine (6.98 mmol) followed by dropwise addition of 2,6-difluorobenzoylchloride (6.98 mmol). The reaction mixture is stirred at room temperature for 5 hours and the product 2,6-difluoro-N-(3-hydroxyphenyl)benzamide is purified by preparative HPLC (Yield: 70%): ^1H NMR (400 MHz, DMSO) δ 10.68 (s, 1H), 9.55 (bs, 1H), 7.57 (m, 1H), 7.28 (m, 1H), 7.23 (m, 2H), 7.12 (t, J = 8 Hz, 1H), 7.05 (m, 1H), 6.54 (m, 1H).

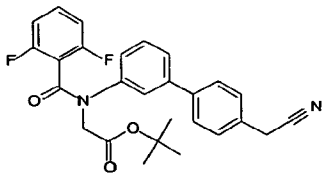
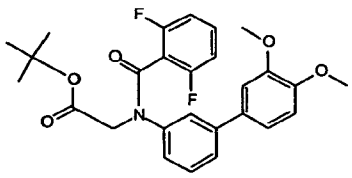
A solution of 2,6-difluoro-N-(3-hydroxyphenyl)benzamide (0.9 mmol) in 4 mL of CH_3CN is treated with potassium carbonate (1.36 mmol) and methyl 4-(bromomethyl)benzoate. The reaction mixture is heated at 80°C for 48 hours. The solvent is evaporated and the O-alkylated product 2,6-difluoro-N-(3-(4-carbomethoxybenzyloxyphenyl)benzamide is obtained

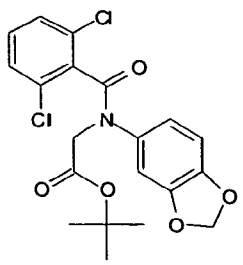
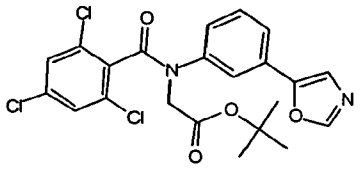
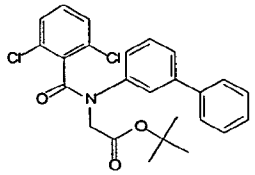
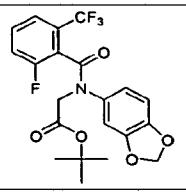
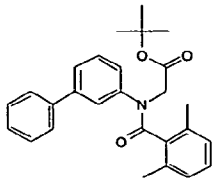
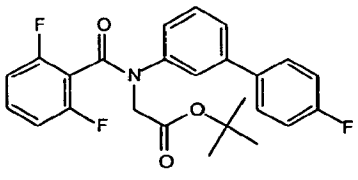
after purification with automated column chromatography (gradient of hexanes and ethyl acetate) (Yield: 69%).

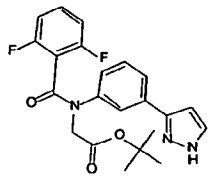
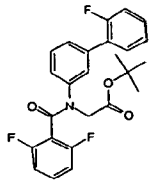
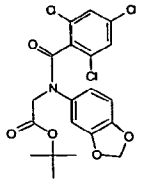
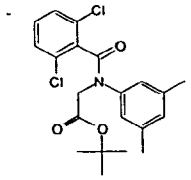
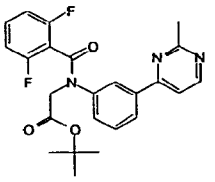
To a solution of 2,6-difluoro-N-(3-(4-carbomethoxybenzyloxyphenyl) benzamide (0.61 mmol) in 4 mL of DMF, first NaH 60% in oil dispersion (0.73 mmol) and after 30 minutes *tert*-butylbromoacetate (0.67 mmol) are added. The reaction is stirred at room temperature for 12 hours. LCMS analysis (10 to 90% CH_3CN) of the reaction mixture reveals that the reaction is complete. DMF is evaporated and the crude *tert*-butyl 2-(2,6-difluoro-N-(3-(4-carbomethoxybenzyloxy)phenyl)benzamido)acetate is finally dissolved in 4 mL of MeOH and treated with LiOH 3M (1.95 mmol). The reaction mixture is purified by preparative LCMS (10 to 90% CH_3CN) to give *tert*-butyl 2-(2,6-difluoro-N-(3-(4-carboxybenzyloxy)phenyl)benzamido)acetate (Yield: 15%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.13 (m, 2H), 6.91 (m, 2H), 6.81 (m, 1H), 6. 70 (m, 2H), 5.05 (s, 2H), 4.45 (s, 2H), 1.51 (s, 9H); MS: (ES^+) 498.1 $(M+1)^+$.

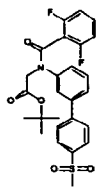
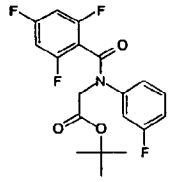
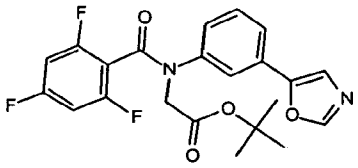
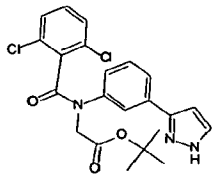
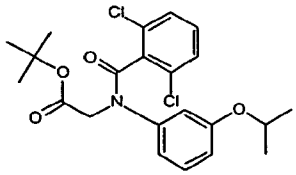
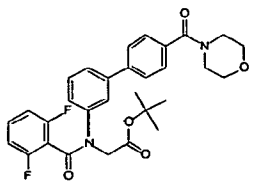
By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

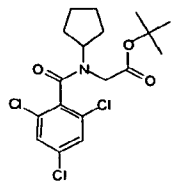
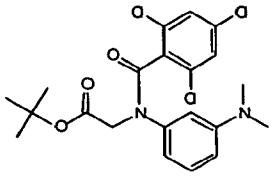
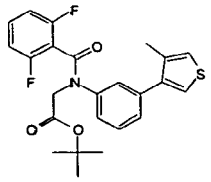
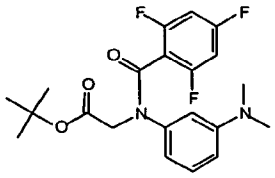
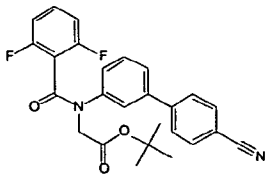
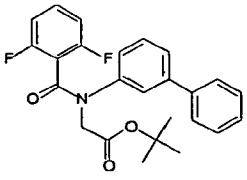
Table 1

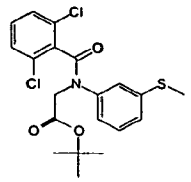
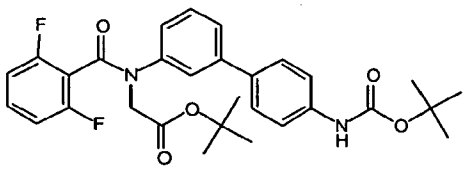
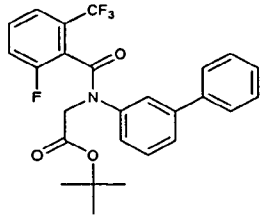
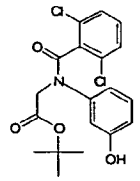
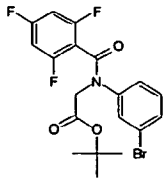
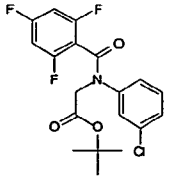
Compound Number	Structure	Physical Data ^1H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
5		485.1 $(M+23)^+$
6		^1H NMR (400 MHz, $CDCl_3$) d 7.49 (s, 1H), 7.36 (m, 1H), 7.26 (m, 3H), 6.98 (dd, J = 2Hz, 1H), 6.91 (m, 2H), 6.72 (m, 2H), 4.51 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H). 1.52 (s, 9H); MS=484.1

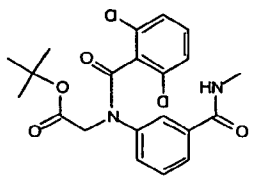
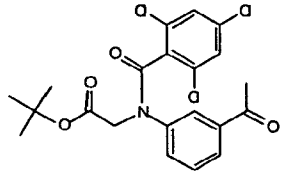
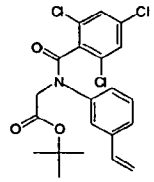
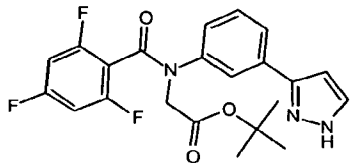
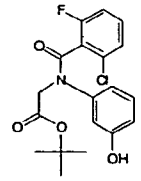
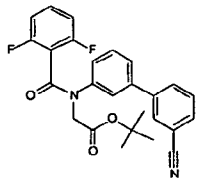
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/ r MS (m/z) $(M+1)^+$
7		424.1
8		481
9		456.1
10		442.1
11		416.2
12		442.1

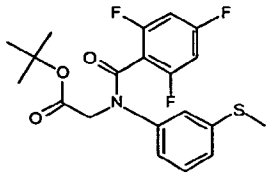
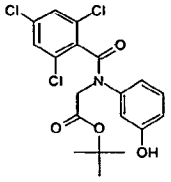
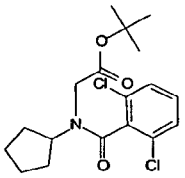
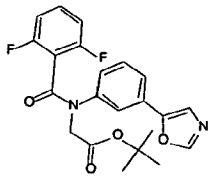
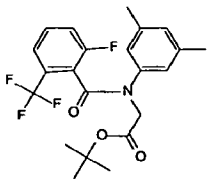
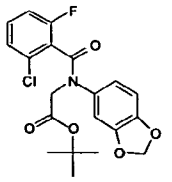
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
13		414.1
14		442.1
15		458
16		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.04 (d, J = 1.6 Hz, 1H), 6.98 (s, 2H), 6.96 (d, J = 2.4 Hz, 1H), 6.71 (s, 1H), 4.40 (s, 2H), 2.10 (s, 6H), 1.43 (s, 9H); MS=408.1
17		425.0 $(M-56)^+$
18		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, J = 5.2 Hz, 1H), 8.20 (s, 1H), 8.09 (dd, J_1 = 1.2 Hz, J_2 = 6 Hz, 1H), 7.49 (m, 3H), 7.28 (m, 1H), 6.85 (m, 2H), 4.65 (s, 2H), 2.95 (s, 3H), 1.69 (s, 9H); MS=440.1

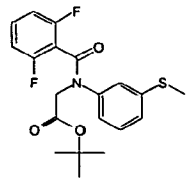
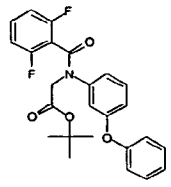
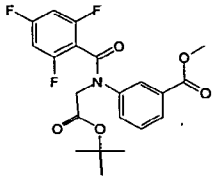
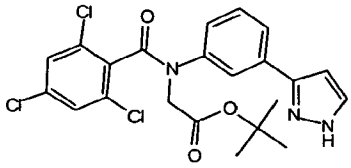
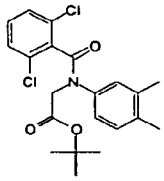
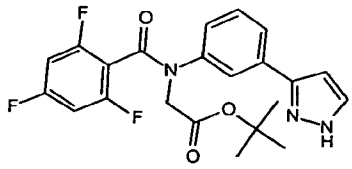
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
19		502.1
20		384.1
21		433.1
22		446.1
23		438.1
24		537.2

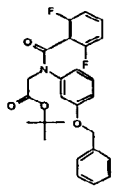
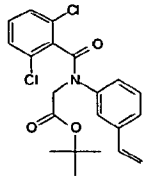
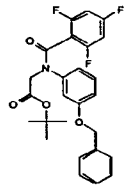
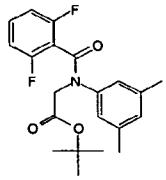
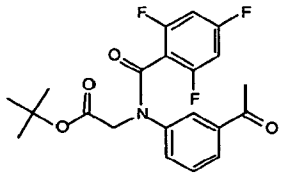
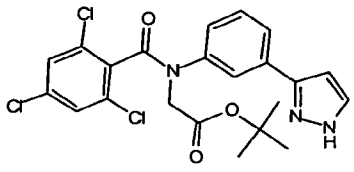
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
25		406
26		457.1
27		444.1
28		409.2
29		449.1
30		424.1

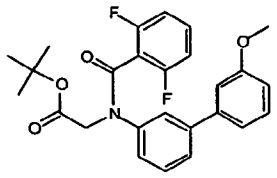
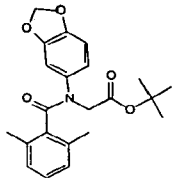
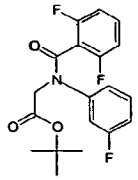
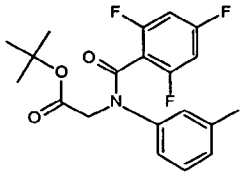
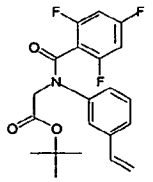
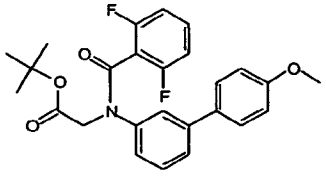
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
31		426
32		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.4 (m, 8H), 6.87 (m, 2H), 6.70 (s, 1H), 4.66 (s, 2H), 1.68 (s, 9H), 1.67 (s, 9H); MS=539.2
33		474.1
34		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (m, 6H), 6.6 (m, 1H), 4.48 (s, 2H), 1.50 (s, 9H); MS=396.1
35		444
36		400.1

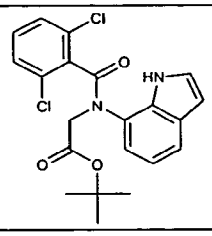
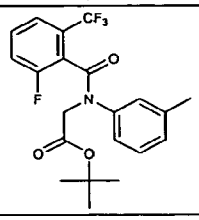
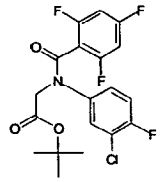
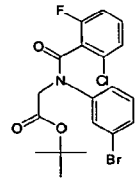
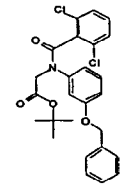
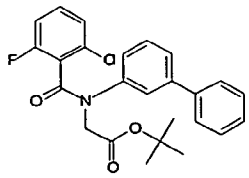
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
37		437.7
38		456
39		440
40		432.1
41		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.68 (m, 1H), 7.55 (m, 2H), 7.42 (m, 2H), 7.20 (m, 1H), 5.04 (d, J = 16.8 Hz, 1H), 4.95 (d, J = 16.8 Hz, 1H), 2.07 (s, 9H); MS=380.1
42		449.1

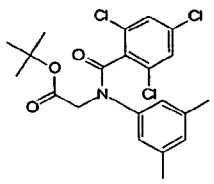
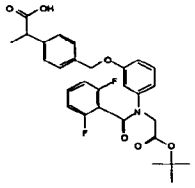
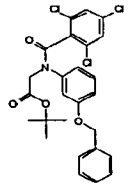
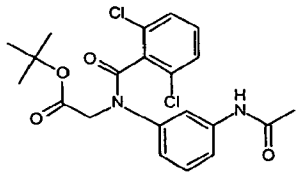
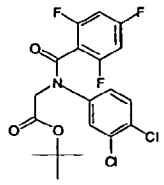
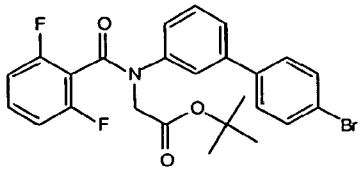
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
43		412.1
44		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 2H), 6.95 (m, 3H), 6.62 (m, 1H), 4.37 (s, 2H), 1.42 (s, 9H); MS=430
45		372.1
46		415.1
47		426.1
48		408.1

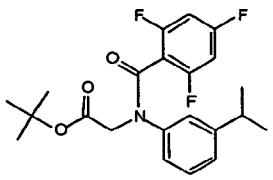
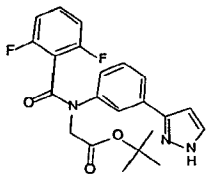
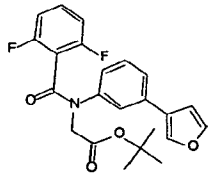
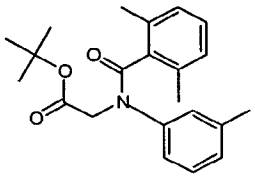
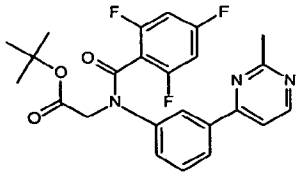
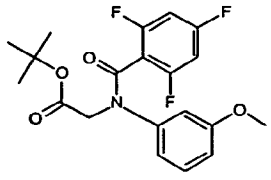
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
49		394.1
50		440.1
51		424.1
52		480
53		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (m, 5H), 6.84 (d, J =8 Hz, 1H), 4.39 (s, 2H), 2.05 (s, 6H), 1.42 (s, 9H); MS=408.1
54		432.1

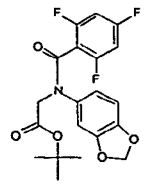
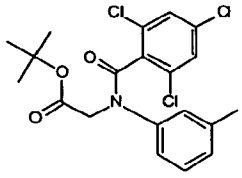
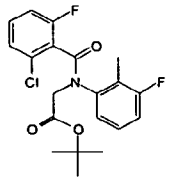
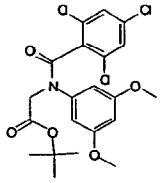
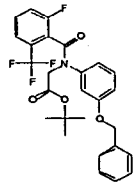
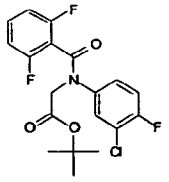
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
55		454.1
56		406
57		472.1
58		376.2
59		352.1 $(M-56)^+$
60		480

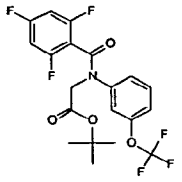
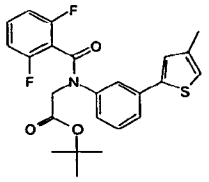
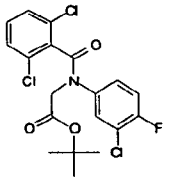
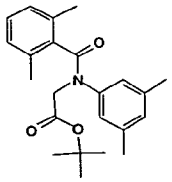
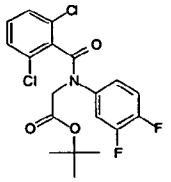
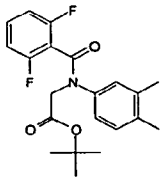
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
61		476.1 $(M+23)^+$
62		384.2
63		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (m, 6H), 6.73 (m, 1H),4.45 (s, 2H), 1.56 (s, 9H); MS=366.1
64		380.1
65		392.1
66		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.23 (m, 3H), 7.11 (m, 3H), 6.82 (d, J = 8.8 Hz, 2H), 6.59 (t, J = 7.2 Hz, 2H), 4.38 (s, 2H), 3.72 (s, 3H), 1.39 (s, 9H); MS=454.1

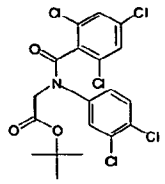
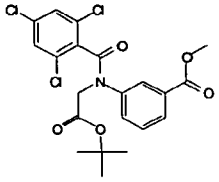
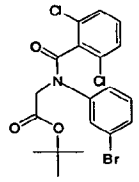
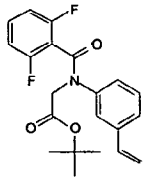
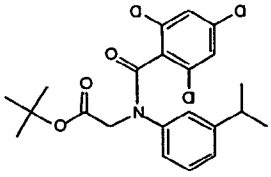
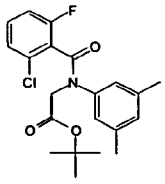
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/ r MS (m/z) $(M+1)^+$
67		419.1
68		412.1
69		418.1
70		442
71		486.1
72		440.1

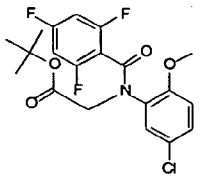
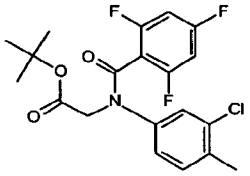
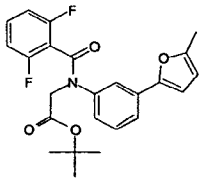
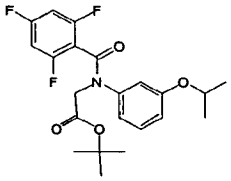
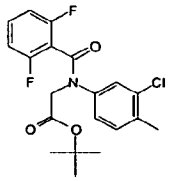
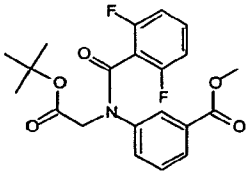
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
73		442
74		526.2
75		520
76		437.1
77		434
78		502

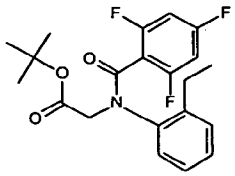
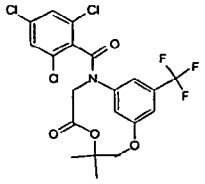
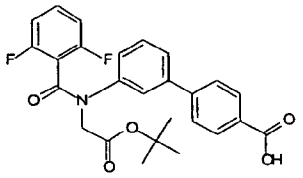
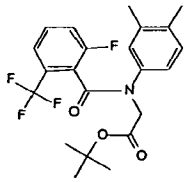
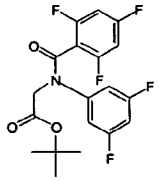
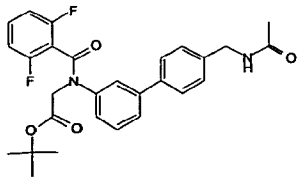
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
79		408.1
80		414.2
81		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.53 (t, J = 1.6 Hz, 1H), 7.36 (s, 1H), 7.33 (m, 4H), 6.79 (m, 2H), 6.65 (m, 1H), 4.57 (s, 2H), 1.59 (s, 9H); MS=414.1
82		354.2
83		458.1
84		396.1

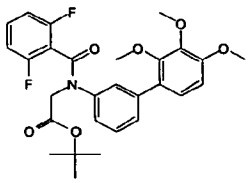
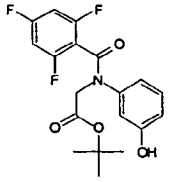
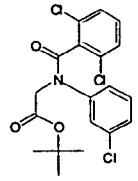
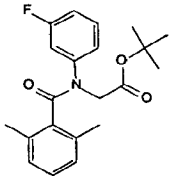
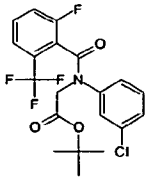
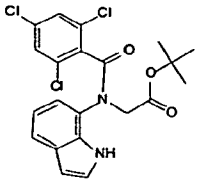
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
85		410.1
86		^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (m, 6H), 4.23 (s, 2H), 2.02 (s, 3H), 1.26 (s, 9H); MS=428
87		396.1
88		474
89		504.1
90		400.1

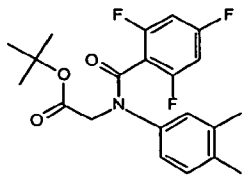
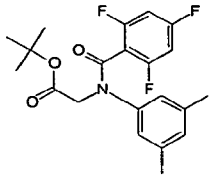
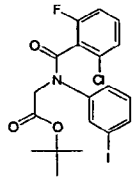
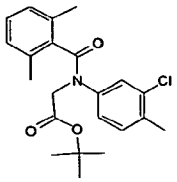
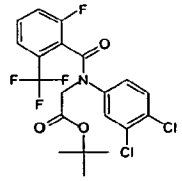
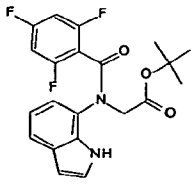
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
91		450.1
92		444.1
93		432
94		368.2
95		416
96		376.1

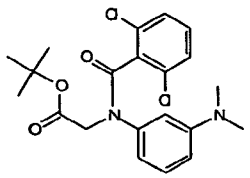
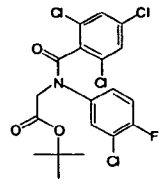
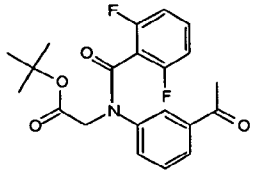
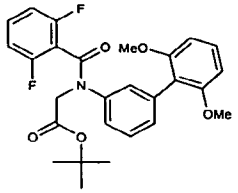
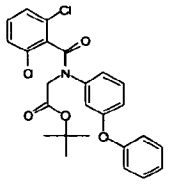
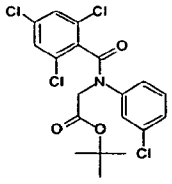
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
97		481.9
98		472
99		458
100		374.1
101		456
102		392.1

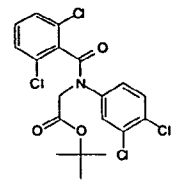
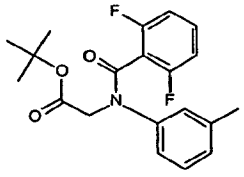
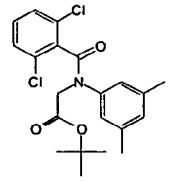
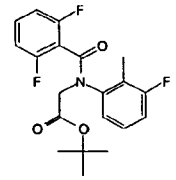
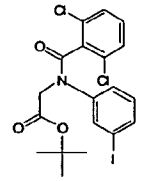
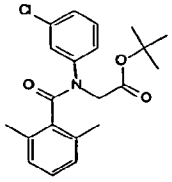
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/ r MS (m/z) $(M+1)^+$
103		430.1
104		414.1
105		428
106		424.2
107		396.1
108		406.2

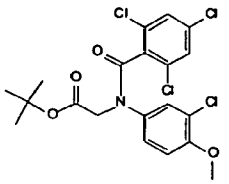
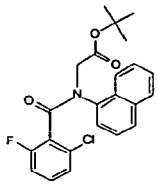
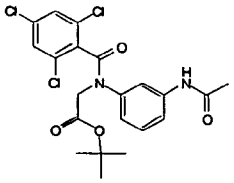
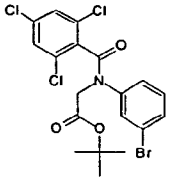
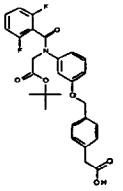
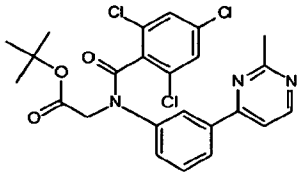
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
109		416.1 $(M+23)^+$
110		512
111		490.1 $(M+23)^+$
112		426.2
113		402.1
114		495.2

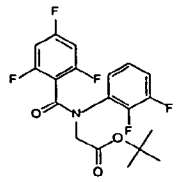
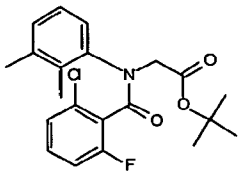
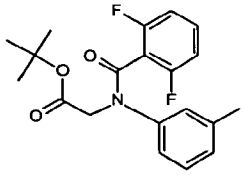
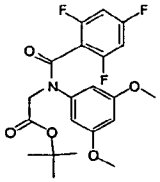
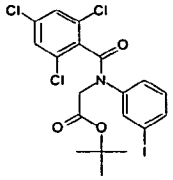
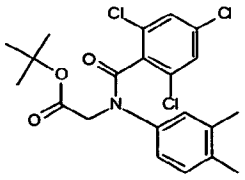
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
115		514.2
116		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (t, J = 8.4 Hz, 1H), 6.78 (s, 2H), 6.69 (d, J = 8 Hz, 1H), 6.48 (t, J = 8 Hz, 2H), 5.85 (bs, 1H), 4.42 (s, 2H), 1.49 (s, 9H); MS=382.1
117		414
118		358.2
119		432.1
120		453

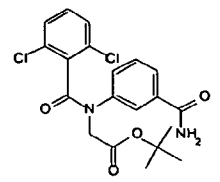
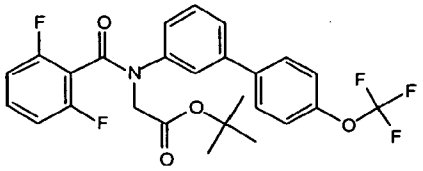
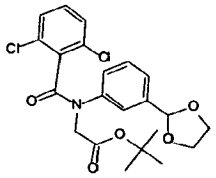
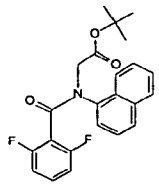
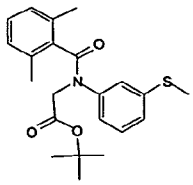
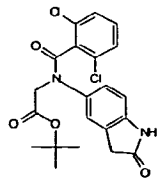
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
121		394.2
122		394.1
123		490
124		388.1
125		466
126		405.1

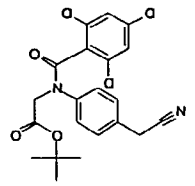
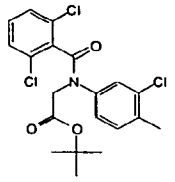
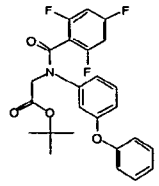
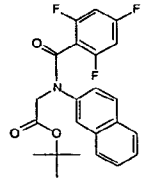
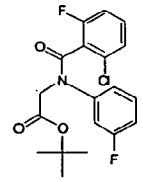
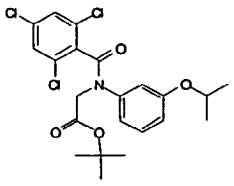
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
127		^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, J = 1.6 Hz, 2H), 6.85 (m, 2H), 6.61 (m, 2H), 6.32 (m, 1H), 4.29 (s, 2H), 2.65 (s, 6H), 1.31 (s, 9H); MS=423.1
128		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 1H), 7.37 (m, 1H), 7.19 (s, 2H), 6.99 (t, J = 8.8 Hz, 1H), 4.44 (s, 2H), 1.49 (s, 9H); MS=466
129		390.1
130		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 6H), 6.69 (t, J = 7.2 Hz, 2H), 6.58 (d. J = 8.4 Hz, 2H), 4.46 (s, 2H), 3.64 (s, 6H), 1,48 (s, 9H); MS=484.1
131		472
132		448

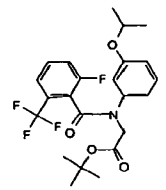
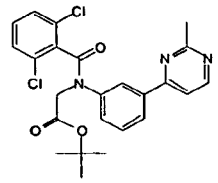
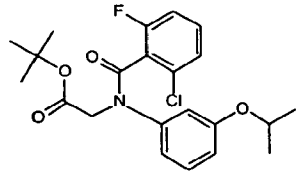
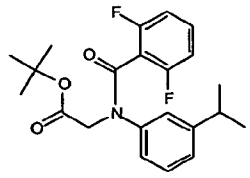
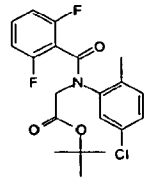
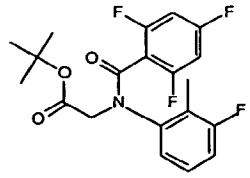
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/ r MS (m/z) $(M+1)^+$
133		448
134		362.2
135		408
136		380.1
137		505.9
138		374.2

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
139		478
140		414.1
141		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.40 (m, 1H), 7.33 (s, 1H), 7.15 (m, 1H), 7.14 (s, 2H), 4.47 (s, 2H), 2.15 (s, 3H), 1.49 (s, 9H); MS=471
142		491.9
143		512.1
144		506.1

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
145		402.9
146		^{1}H NMR (400 MHz, MeOD) δ 6.94 (m, 6H), 4.45 (d, J = 16.8 Hz, 1H), 4.41 (d, J = 16.8 Hz, 1H), 2.1 (s, 6H), 1.51 (s, 9H); MS=392.1
147		384.1 $(M+23)^+$
148		426.1
149		540.1
150		442

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
151		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (t, J = 1.6 Hz, 1H), 7.58 (m, 2H), 7.23 (t, J = 8 Hz, 1H), 7.01 (m, 3H), 5.95 (bs, 1H), 5.62 (bs, 1H), 4.46 (s, 2H), 1.41 (s, 9H); MS=445 $(M+23)^+$
152		508.1
153		452.1
154		398.2
155		386.2
156		435.1

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/ r MS (m/z) $(M+1)^+$
157		453
158		428
159		458.1
160		416.1
161		382.1
162		472

Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz ($CDCl_3$) and/or MS (m/z) $(M+1)^+$
163		456.1
164		472.1
165		422.1
166		390.1
167		396.1
168		398.1

Assay1 - Transcriptional Assay

Transfection assays are used to assess the ability of compounds of the invention to modulate the transcriptional activity of the LXRs. Briefly, expression vectors for chimeric proteins containing the DNA binding domain of yeast GAL4 fused to the ligand-binding domain (LBD) of either LXRα or LXRβ are introduced via transient transfection into mammalian cells, together with a reporter plasmid where the luciferase gene is under the control of a GAL4 binding site. Upon exposure to an LXR modulator, LXR transcriptional activity varies, and this can be monitored by changes in luciferase levels. If transfected cells are exposed to an LXR agonist, LXR-dependent transcriptional activity increases and luciferase levels rise.

293T human embryonic kidney cells ($8x10^6$) are seeded in a $175cm^2$ flask 2 days prior to the start of the experiment in 10% FBS, 1% Penicillin/Streptomycin/Fungizome, DMEM Media. The transfection mixture for chimeric proteins is prepared using GAL4-LXR LBD expression plasmid (4μg), UAS-luciferase reporter plasmid (5μg), Fugene (3:1 ratio; 27μL) and serum-free media (210μL). The transfection mixture is incubated for 20 minutes at room temperature. The cells are harvested by washing with PBS (30ml) and then dissociating using trypsin (0.05%; 3ml). The trypsin is inactivated by the addition of assay media (DMEM, lipoprotein-deficient fetal bovine serum (5%), statin (e.g. lovastatin 7.5μM), and mevalonic acid (100μM)) (10ml). The cells are counted using a 1:10 dilution and the concentration of cells adjusted to 160,000cells/ml. The cells are further incubated for 30 minutes at room temperature with periodic mixing by inversion. Transfection mixtures are added to the cells, and cells (50μl/well) are then plated into 384 white, solid-bottom, TC-treated plates. The cells are further incubated at 37°C, 5.0% CO_2 for 24 hours. A 12-point series of dilutions (half-log serial dilutions) are prepared for each test compound in DMSO with a starting concentration of compound of 1μM. Test compound (500nl) is added to each well of cells in the assay plate and the cells are incubated at 37°C, 5.0% CO_2 for 24 hours. The cell lysis/luciferase assay buffer, Bright-Glo™ (25%; 25μl; Promega), is added to each well. After a further incubation for 5 minutes at room temperature, the luciferase activity is measured.

Raw luminescence values are normalized by dividing them by the value of the DMSO control present on each plate. Normalized data is visualized using XLfit3 and dose-response curves are fitted using a 4-parameter logistic model or sigmoidal single-site dose-response equation (equation 205 in XLfit3.05). EC50 is defined as the concentration at which the

compound elicits a response that is half way between the maximum and minimum values. Relative efficacy (or percent efficacy) is calculated by comparison of the response elicited by the compound with the maximum value obtained for a reference LXR modulator.

Assay2 - FRET Co-activator Recruitment Assay

A FRET assay is used to assess the ability of a compound of the invention to bind directly to the LXR ligand-binding domain (LBD) and promote the recruitment of proteins that potentiate the transcriptional activity of LXRs (e.g. co-activators). This cell-free assay uses a recombinant fusion protein composed of the LXR LBD and a tag (e.g. GST, His, FLAG) that simplifies its purification, and a synthetic biotinylated peptide derived from the nuclear receptor interacting domain of a transcriptional co-activator protein, such as steroid receptor co-activator 1 (SRC-1). In one format, the tagged LBD fusion protein can be labeled using an antibody against the LBD tag coupled to europium (e.g. EU-labeled anti-GST antibody), and the co-activator peptide can be labeled with allophycocyanin (APC) coupled to streptavidin. In the presence of an agonist for LXR, the co-activator peptide is recruited to the LXR LBD, bringing the EU and APC moieties in close proximity. Upon excitation of the complex with light at 340nM, EU absorbs and transfers energy to the APC moiety resulting in emission at 665 nm. If there is no energy transfer (indicating lack of EU-APC proximity), EU emits at 615nm. Thus the ratio of the 665 to 615nm light emitted gives an indication of the strength of co-activator peptide recruitment, and thus of agonist binding to the LXR LBD.

Fusion proteins, amino acids 205-447 (Genbank NM_005693) for LXRα and amino acids 203-461 (NM_007121for β) for LXRβ, were cloned in-frame at the Sal1 and Not1 sites of pGEX4T-3 (27-4583-03 Amersham Pharmacia Biotech). A biotinylated peptide sequence was derived from SRC-1 (amino acids 676 to 700): biotin-CPSSHSSLTERHKILHRLLQEGSPSC-OH.

A master mix is prepared (5nM GST-LXR-LBD, 5nM Biotinylated SRC-1 peptide, 10nM APC-Streptavidin (Prozyme Phycolink streptavidin APC, PJ25S), and 5n MEU-Anti-GST Antibody) in FRET buffer (50mM Tris pH 7.5, 50mM KCl 1mM DTT, 0.1% BSA). To each well of a 384 well plate, 20μL of this master mix is added. Final FRET reaction: 5nM fusion protein, 5nM SRC-1 peptide, 10nM APC-Streptavidin, 5nm EU-Anti-GST Antibody

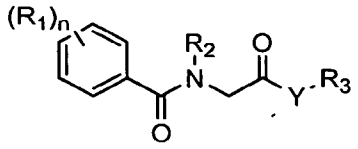
(PerkinElmer AD0064). Test compounds are diluted in half-log, 12-point serial dilutions in DMSO, starting at 1mM and 100nL of compound is transferred to the master mix for a final concentration of 5μM-28pM in the assay wells. Plates are incubated at room temperature for 3 hours and fluorescence resonance energy transfer read. Results are expressed as the ratio of APC fluorescence to EU fluorescence times one thousand.

The ratio of 665nm to 615nm is multiplied by a factor of 1000 to simplify data analysis. DMSO values are subtracted from ratios to account for background. Data is visualized using XLfit3 and dose-response curves are fitted using a 4-parameter logistic model or sigmoidal single-site dose-response equation (equation 205 in XLfit3.05). EC50 is defined as the concentration at which the compound elicits a response that is half way between the maximum and minimum values. Relative efficacy (or percent efficacy) is calculated by comparison of the response elicited by the compound with the maximum value obtained for a reference LXR modulator.

Compounds of Formula I, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example, as indicated by the *in vitro* tests described in this application. It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. A compound of Formula I:



in which:

Y is chosen from –O–, –NR_4– and –S–; wherein R_4 is chosen from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl-C_{0-4}alkyl, C_{3-8}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl;

n is chosen from 0, 1, 2, 3 and 4;

R_1 is chosen from halo, hydroxy, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy, -$XC(O)R_4$, -$XOC(O)R_4$, -$XC(O)OR_4$, -XOR_4, -$XS(O)_2R_4$, -$XS(O)R_4$, -XSR_4, -XNR_4R_8, -$XC(O)NR_4R_8$, -$XNR_4C(O)R_4$, -$XNR_4C(O)OR_4$, -$XNR_4C(O)NR_4R_8$, -$XNR_4C(NR_4R_4)NR_4R_8$, -$XP(O)(OR_4)OR_4$, -$XOP(O)(OR_4)OR_4$, -$XS(O)_2NR_4R_8$, -$XS(O)NR_4R_8$, -$XSNR_4R_8$, -$XNR_4S(O)_2R_4$, -$XNR_4S(O)R_4$, -XNR_4SR_4, -$XNR_4C(O)NR_4R_8$, - and -$XC(O)SR_4$; wherein X is a bond or C_{1-6}alkylene; and R_4 and R_8 are independently chosen from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl-C_{0-4}alkyl, C_{3-8}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; or R_4 and R_8 together with the nitrogen atom to which R_4 and R_8 are attached form C_{5-10}heteroaryl or C_{3-8}heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_4 or the combination of R_4 and R_8 is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{3-8}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any aryl-alkyl, heteroaryl-alkyl, cycloalkyl-alkyl or heterocycloalkyl-alkyl of R_2 is optionally substituted by 1 to 4 radicals chosen from halo, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{3-8}heteroaryl, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, -$XC(O)R_5$, -$XOC(O)R_5$, -$XC(O)OR_5$, -XOR_5, -$XS(O)_2R_5$, -$XS(O)R_5$, -XSR_5, -XNR_5R_8, -$XC(O)NR_5R_8$, -

$XNR_5C(O)R_5$, $-XNR_5C(O)OR_5$, $-XNR_5C(O)NR_5R_8$, $-XNR_5C(NR_5R_8)NR_5R_8$, $-XP(O)(OR_5)OR_5$, $-XOP(O)(OR_5)OR_5$, $-XS(O)_2NR_5R_8$, $-XS(O)NR_5R_8$, $-XSNR_5R_8$, $-XNR_5S(O)_2R_5$, $-XNR_5S(O)R_5$, $-XNR_5SR_5$, $-XNR_5C(O)NR_5R_8$, $-XR_6$ and $-XOR_7$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent of R_2 is optionally substituted by 1 to 3 radicals chosen from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-XC(O)R_5$, $-XOC(O)R_5$, $-XC(O)OR_5$, $-XOR_5$, $-XS(O)_2R_5$, $-XS(O)R_5$, $-XSR_5$, $-XNR_5R_8$, $-XC(O)NR_5R_8$, $-XNR_5C(O)R_5$, $-XNR_5C(O)OR_5$, $-XNR_5C(O)NR_5R_8$, $-XNR_5C(NR_5R_8)NR_5R_8$, $-XP(O)(OR_5)OR_5$, $-XOP(O)(OR_5)OR_5$, $-XS(O)_2NR_5R_8$, $-XS(O)NR_5R_8$, $-XSNR_5R_8$, $-XNR_5S(O)_2R_5$, $-XNR_5S(O)R_5$, $-XNR_5SR_5$, $-XNR_5C(O)NR_5R_8$, $-XR_6$ and $-XOR_7$; wherein X is a bond or C_{1-6}alkylene; R_5 and R_8 are independently chosen from hydrogen and C_{1-6}alkyl; or R_5 and R_8 together with the nitrogen to which R_5 and R_8 are attached form C_{3-8}heteroaryl or C_{3-8}heterocycloalkyl; wherein any heteroaryl or heterocycloalkyl of the combination of R_5 and R_8 is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; R_6 is chosen from cyano and C_{1-6}alkyl; and R_7 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{3-8}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_7 is optionally further substituted by $-XC(O)OR_5$; wherein R_5 is chosen from hydrogen and C_{1-6}alkyl;

R_3 is chosen from C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which n is chosen from 0, 1, 2 and 3; Y is –O–;

R_1 is chosen from halo, C_{1-6}alkyl and halo-substituted-C_{1-6}alkyl;

R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{3-8}heteroaryl-C_{0-4}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; wherein any aryl-alkyl, heteroaryl-alkyl or cycloalkyl-alkyl of R_2 is optionally substituted by 1 to 3 radicals chosen from halo, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{3-8}heteroaryl, C_{3-8}heterocycloalkyl, $-XC(O)R_5$, $-XC(O)OR_5$, $-XOR_5$, $-XSR_5$, $-XNR_5R_8$, $-XC(O)NR_5R_8$, $-XNR_5C(O)R_5$, $-XR_6$ and $-XOR_7$; wherein any aryl, heteroaryl or heterocycloalkyl substituent of R_2 is optionally

substituted by 1 to 3 radicals chosen from halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, -$XC(O)OR_5$, -XOR_5, -$XS(O)_2R_5$, -$XNR_5C(O)R_5$, -$XNR_5C(O)OR_5$, $-XR_6$ and -$XC(O)R_7$; wherein X is a bond or C_{1-6}alkylene; R_5 and R_8 are independently chosen from hydrogen and C_{1-6}alkyl; R_6 is cyano; and R_7 is C_{6-10}aryl-C_{0-4}alkyl optionally further substituted by $-XC(O)OR_5$; wherein R_5 is chosen from hydrogen and C_{1-6}alkyl; and R_3 is C_{1-6}alkyl.

3. The compound of claim 1 in which R_1 is chosen from halo, methyl, ethyl and trifluoromethyl; and R_3 is *t*-butyl.

4. The compound of claim 1 in which R_2 is chosen from phenyl, benzo[1,3]dioxolyl, cyclopentyl, 1H-indolyl, naphthyl and 2-oxo-2,3-dihydro-1H-indol-5-yl; wherein any aryl-alkyl, heteroaryl-alkyl or cycloalkyl-alkyl of R_2 is optionally substituted by 1 to 3 radicals chosen from halo, hydroxy, methoxy, trifluoro-methoxy, trifluoro-methyl, methyl, phenyl, oxazolyl, pyrazolyl, pyrimidinyl, amino-carbonyl, dimethyl-amino, thiophenyl, methyl-sulphanyl, methyl-formamidyl, methyl-carbonyl, ethenyl, phenoxy, methoxy-carbonyl, benzoxy, isopropyl, furanyl, isopropyloxy, [1,3]dioxolanyl and cyano-methyl; wherein any aryl, heteroaryl or heterocycloalkyl substituent of R_2 is optionally substituted by 1 to 3 radicals chosen from halo, methyl, cyano, carboxy, carboxy-methyl, cyano-methyl, methoxy, phenyl, acetyl-amino, methyl-sulphonyl, methoxy-carbonyl-amino, 1-carboxy-ethyl and trifluoro-methoxy.

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

6. A method for treating a disease in an animal in which modulation of LXR activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

7. The use of a compound of claim 1 in the manufacture of a medicament for treating a disease in an animal in which LXR activity contributes to the pathology and/or symptomology of the disease.

5

COMPOUNDS AND COMPOSITIONS AS LXR MODULATORS

ABSTRACT OF THE DISCLOSURE

The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of liver X receptors (LXRs).